

DISCLAIMER: These guidelines were prepared jointly by the Surgical Critical Care and Medical Critical Care Services at Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

# VENOUS THROMBOPROPHYLAXIS IN OBESITY

## SUMMARY

Obesity is associated with an increased rate of venous thromboembolism (VTE) among trauma and surgical patients. The optimal dosing of enoxaparin for VTE prophylaxis in this population is not clearly defined as the relationship between monitoring of therapy and outcomes is lacking, obese patients may not follow a predictable dose response, and they often have multiple other risk factors for VTE. Non-standard enoxaparin dosing should therefore be considered in these patients to reduce their risk of VTE.

## RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **In trauma and surgical patients with a BMI >35 kg/m<sup>2</sup>, standard enoxaparin dosing (30 mg SQ twice daily) is inadequate; such patients should receive 40 mg SQ twice daily**
- **Level 3**
  - **Standard heparin and enoxaparin dosing should be used in traumatic brain injury patients until the safety of weight-based therapy has been documented**
  - **Non-standard high-dose enoxaparin dosing does not increase the risk of bleeding**
  - **In patients with BMI > 30 kg/m<sup>2</sup>, consider monitoring anti-Xa levels to ensure appropriate prophylaxis (target anti-Xa level: 0.1-0.3 IU/mL)**

## INTRODUCTION

VTE is a serious complication in hospitalized patients, contributing to increased hospital length of stay, cost, morbidity, and mortality. Among the many risk factors for VTE are surgery, trauma, history of malignancy, and immobility. Obesity, which is increasing in incidence worldwide, is also a well-established risk factor for VTE (1). For every 10-unit increase in BMI, there is a 37% increase in the risk of VTE among bariatric surgery patients (2). Trauma, a well-established risk factor for VTE, is associated prolonged immobility as well as the potential of serious bleeding risk. Chemical thromboprophylaxis against VTE in trauma patients is commonly achieved with subcutaneous enoxaparin. Enoxaparin is a low molecular weight heparin routinely given at a standard 30 mg twice-daily dosage--or in a single 40 mg dose daily—and favored for the ease of administration and its favorable and predictable pharmacokinetics. It inactivates Factor Xa to a greater extent than unfractionated heparin, and due to its predictable efficacy, anti-Xa levels are not routinely monitored (3). Current research suggests that target anti-Xa levels may not be achieved in many patients with “standard” enoxaparin dosing regimens. Thus, when standard enoxaparin dosages are administered to obese trauma patients, they may not be achieving the desired therapeutic effect (4-6). An evidence-based approach to the dosing of low molecular weight heparin is needed to provide appropriate thromboprophylaxis in high-risk obese trauma patients.

## EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

## LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

## LITERATURE REVIEW

There are no published multi-center, randomized controlled trials of high quality evaluating the dose of enoxaparin for VTE prophylaxis in obese trauma patients.

### Anti-Xa Level

Variation exists in the methods used to assess anti-Xa levels. Early recommendations were based on “trough” levels, however more recent studies use “peak” levels. Other studies have measured anti-Xa levels at variable time points making comparison of effect among studies difficult (7-11). The American College of Chest Physician guidelines recommend measuring peak anti-Xa levels 4 hours after dosing (3). The generally accepted target peak anti-Xa level for prophylactic VTE anticoagulation is 0.2-0.5 IU/ml (9).

Multiple studies demonstrate an inverse relationship between BMI and anti-Xa level following administration of enoxaparin (4-6,8-10). A prospective study with 61 patients found most patients actually had a sub-target anti-Xa level and that lower anti-Xa levels were more likely to be seen in obese patients (5). Celik et al. observed a linear relationship between achieved anti-Xa level and patient weight when three groups (<110 kg, 110-150 kg, and >150 kg) were all given the same “high-dose” prophylactic enoxaparin regimen (40 mg BID) (7). Patients with the greatest weight had the lowest anti-Xa levels.

There is also concern that standard dose regimens may not achieve target levels in all critically ill trauma and surgical patients. In a recent prospective study, 54 critically ill trauma and surgery patients were given a standard dose regimen of enoxaparin 30 mg BID and their anti-Xa levels were monitored. They found that standard doses led to low anti-Xa levels in half of the patients and this was associated with higher rates of VTE (4). A prospective study in 84 burn patients found a low incidence of VTE (2.4%) and no increase in bleeding events when an escalating dosage regimen guided by anti-Xa level monitoring was utilized (13). In a prospective observational study of trauma patients, Constantini et al. found that 70% of patients receiving standard enoxaparin dosing failed to achieve target anti-Xa levels and were more likely to be both male and obese (5).

There is increasing evidence that adjusting enoxaparin dosing for a patient’s weight or BMI increases the likelihood a patient will achieve target anti-Xa levels. Freeman et al. prospectively studied 31 medical patients with BMI >40 kg/m<sup>2</sup> (9). Patients were given one of three different weight based regimens of enoxaparin: 40 mg daily, weight-based low-dose (0.4 mg/kg), or weight-based high-dose (0.5 mg/kg). The weight-based high-dose enoxaparin regimen resulted in a target anti-Xa level of 0.2-0.5 IU/ml in 85% of patients. This is in comparison to 82% of patients in the standard dose group and 36% in the weight-based low-dose group. Bickford et al. evaluated a weight-based enoxaparin regimen and found a dose of 0.5 mg/kg resulted in 86% of patients achieving therapeutic anti-Xa levels (6). They did not observe any bleeding complications and had no patients develop symptomatic pulmonary embolism. Rowan et al. showed that increasing the dose of enoxaparin from 30 mg BID to 40 mg BID improved the number of patients that reached target anti-Xa levels from 9% to 42% after the third dose of enoxaparin; however, despite the higher dose, more than half of bariatric surgery patients failed to achieve target anti-Xa levels (10). Kopelman et al. also showed high-dose enoxaparin improved the number of obese trauma patients that reached target anti-Xa levels (12). Borkgren-Okonek et al. examined anti-Xa levels in 223 obese patients, stratifying patients by BMI and adjusting their dose accordingly: patients with BMI <50 kg/m<sup>2</sup> received 40 mg BID, and BMI >50 kg/m<sup>2</sup> received 60 mg BID. They found anti-Xa levels to be within target range after the third dose in 79% and 69% of patients respectively. The study had 7.6% of patients undergo a workup for VTE and had only one VTE event - that patient eventually was found to have hyperhomocysteinemia (11).

### Anti-Xa level and VTE incidence

Despite the evidence that weight-based enoxaparin dosing improves the likelihood that patients will achieve a target anti-Xa level, it is unclear what anti-Xa level correlates with decreased VTE risk. This is explicitly acknowledged by the College of American Chest Physicians in their VTE prophylaxis guidelines (3). This is partly based upon the recognition that it remains unclear whether trough or peak anti-Xa levels are better measures of risk of bleeding and thrombosis. In one of the earliest studies by Levine et al., trough anti-Xa levels correlated with VTE and hemorrhage, however the study’s results have not been fully replicated in subsequent trials (3,14,15). A number of studies examining dosing regimens either examined anti-Xa

levels, or VTE incidence, but often are not powered to assess both. Further appropriately powered studies will be needed to clarify the relationship between anti-Xa levels and VTE incidence.

#### Non-Standard Dose Enoxaparin in Obese Patients and VTE Incidence

Despite the lack of literature directly examining the relationship between non-target anti-Xa levels and VTE occurrence, there is support for non-standard enoxaparin dosing in improving VTE incidence in obese surgical and trauma patients. In a small study of obese trauma patients that was not adequately powered to show a difference, high-dose enoxaparin trended towards but did not significantly decrease VTE rate (12). The PROBE study retrospectively surveyed the enoxaparin dosing regimens at five different bariatric surgery centers. They determined that the center that used a high dose enoxaparin (40 mg BID) regimen had the lowest rates of VTE compared to the other centers with increased risk of adverse events (16). In a study of 481 morbidly obese bariatric surgery patients with a mean BMI of 50 kg/m<sup>2</sup>, who were given two different dosing regimens (30 mg BID vs. 40 mg BID) with the primary outcome of thrombosis, it was found that the rate of VTE in the standard dose regimen was 5.4%, and the rate of VTE in the high-dose regimen was 0.6% (17).

In a retrospective cohort study evaluating greater than 9000 trauma patients with weight >100 kg, assigned to either standard (40 mg daily) or high-dose (40 mg BID) enoxaparin, Wang et al. found that high-dose thromboprophylaxis nearly halves the rate of VTE in patients with a BMI greater than 40 kg/m<sup>2</sup> (1.48% vs 0.77%, OR 0.52, p=0.05, 95% confidence interval [CI] 0.27-1.00). In patients with BMI <40 kg/m<sup>2</sup>, there was no demonstrated benefit to high-dose thromboprophylaxis, even though those patients had weights greater than 100 kg. They also conducted an analysis of bleeding complications, which found that there was no statistically significant increase in bleeding complications with high-dose thromboprophylaxis for BMI both less than and greater than 40 kg/m<sup>2</sup> (18).

## **DISCUSSION**

The literature examining anti-Xa levels uses three different dosing approaches: 1) weight-adjusted; 2) non-standard high-dose enoxaparin (40 mg BID); and 3) anti-Xa level-adjusted enoxaparin dosing. The literature demonstrating a decrease in VTE outcomes among obese patients primarily uses non-standard high-dose enoxaparin as its intervention (12,16-18).

A recent literature review by Shelkrot et al. looking at eight studies in patients with BMI >40 kg/m<sup>2</sup> concluded that the strongest evidence for thromboprophylaxis in obese patients is enoxaparin 40 mg BID (19). These studies demonstrated increased success in achieving target anti-Xa levels and variably demonstrated a trend towards lower VTE rates.

There are additional advantages to using high dose enoxaparin in contrast to a weight-adjusted or anti-Xa level-adjusted enoxaparin strategy: ease of dosing, decreased chance of medication error, and ease of dispensing. This remains however an area where additional research is needed, as the studies evaluating a weight-based regimen have not been adequately powered or directly compared to a high-dose regimen. A recent internal review of our experience with pulmonary embolism and obesity identified a seven-fold higher risk of pulmonary embolism among patients with a BMI > 35.

For this reason, we recommend high dose enoxaparin—40 mg BID—for trauma and surgical patients with a BMI >35 kg/m<sup>2</sup> (Class II recommendation). However, given the ease of reversal, consideration should be given to using unfractionated heparin in patients with a high bleeding risk.

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